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**BE CH DE FR GB IT LI NL**(71) Applicant: **AJINOMOTO CO., INC.**  
**15-1, Kyobashi 1-chome, Chuo-ku**  
**Tokyo 104(JP)**(72) Inventor: **Abe, So, c/o Cent.Res.Lab.**  
**Ajinomoto Co.,Ltd., No.1-1 Suzuki-cho,**  
**Kawasaki-ku**  
**Kawasaki-shi, Kanagawa-ken(JP)**  
Inventor: **Kishimoto, Shinichi, c/o**  
**Cent.Res.Lab.**  
**Ajinomoto Co.,Ltd., No.1-1 Suzuki-cho,**  
**Kawasaki-ku**  
**Kawasaki-shi, Kanagawa-ken(JP)**  
Inventor: **Kato, Toshihisa, c/o Cent.Res.Lab.**  
**Ajinomoto Co.,Ltd., No.1-1 Suzuki-cho,**  
**Kawasaki-ku**  
**Kawasaki-shi, Kanagawa-ken(JP)**  
Inventor: **Takeda, Hideo, c/o Cent.Res.Lab.**  
**Ajinomoto Co.,Ltd., No.1-1 Suzuki-cho,**  
**Kawasaki-ku**  
**Kawasaki-shi, Kanagawa-ken(JP)**(74) Representative: **Strehl, Schübel-Hopf,**  
**Groening**  
**Maximilianstrasse 54 Postfach 22 14 55**  
**W-8000 München 22(DE)**(54) **Method of crystallizing alpha-L-aspartyl-L-phenylalanine methyl ester.**(57) In crystallizing  $\alpha$ -APM from its aqueous solvent in a crystallizer, the pressure in the crystallizer is held at not higher than atmospheric pressure, a water or water/alcohol mixed solution of  $\alpha$ -APM is fed into the crystallizer with stirring so that the solvent is vaporized, and the crystallization solution is cooled and crystallized by the latent heat of vaporization or is heated so as to prevent super-cooling.

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## BACKGROUND OF THE INVENTION

The present invention relates to a method of preparing  $\alpha$ -L-aspartyl-L-phenylalanine methyl ester (hereinafter referred to as " $\alpha$ -APM") which is useful as a sweetener and relates to an improved method of crystallizing  $\alpha$ -APM from a solution of  $\alpha$ -APM.

$\alpha$ -APM of the present invention is a dipeptide sweetener having a sweetness about 200 times that of sucrose (cane sugar). Because of its good sweetening properties and the low calory content, it is widely used as a diet sweetener, and the world-wide demand for it is estimated to be over 10,000 tons by 1995.

$\alpha$ -APM is produced industrially by several methods. One method of obtaining  $\alpha$ -APM is to react a N-substituted aspartic acid anhydride and a phenylalanine methyl ester in an organic solvent followed by removal of the N-substituent from the product by a conventional method (U.S. Patent 3,786,039). The thus formed  $\alpha$ -APM containing impurities is brought into contact with a hydrohalogenic acid to obtain  $\alpha$ -APM hydro halide which is neutralized to obtain  $\alpha$ -APM. A second method of obtaining  $\alpha$ -APM is to methyl-esterify  $\alpha$ -L-aspartyl-L-phenylalanine in a mixed solvent comprising water, methanol and hydrochloric acid to obtain  $\alpha$ -APM hydrochloride, and then neutralize the hydrochloride to obtain  $\alpha$ -APM (Japanese Patent Application Laid-Open No. 53-82752). A third method of obtaining  $\alpha$ -APM is to condense an N-substituted aspartic acid and a phenylalanine methyl ester in the presence of an enzyme and thereafter remove the N-substituent from the product (Japanese Patent Application Laid-Open No. 55-135595).

In all of the above-mentioned methods,  $\alpha$ -APM is finally crystallized by cooling from an aqueous solution having a relatively high temperature, then the resulting  $\alpha$ -APM crystals are separated and dewatered in a solid-liquid separator, such as a centrifugal separator, and thereafter the thus separated crystals are dried. The cooling crystallization is generally carried out in a stirring crystallizer having a heat transfer surface for cooling or in a crystallizer equipped with an external heat exchanger and an external circulation system, such as pumps.

When crystallization of  $\alpha$ -APM is carried out by cooling an  $\alpha$ -APM-containing solution in a conventional forced flow system crystallizer with a stirring means or external circulation means, the solution always gives fine needle-like  $\alpha$ -APM crystals having poor filterability and dewaterability. In addition, in such a system, numerous crystals precipitate and consolidate on the cooling heat transfer surface, whereby the heat transfer efficiency is markedly lowered. Therefore, to remove the consoli-

dated crystals ("scale"), the operation of the crystallizer must be frequently stopped.

As a means of overcoming this problem, there is known a method of cooling an aqueous solution of  $\alpha$ -APM by conductive heat transfer without effecting any forced flow such as mechanical stirring, to form a pseudo solid phase, optionally followed by further cooling the system (Japanese Patent Application Laid-Open No. 58-177952). In accordance with this method, peeling of the crystals from the cooling surface is extremely easy when discharging the crystal layer (sherbet-like pseudo solid phase), and  $\alpha$ -APM crystals having improved filterability and dewaterability in the successive solid-liquid separation step can be obtained. However, where existing or widely-used crystallization equipment is employed, the cooling takes a long time, the efficiency of the method is poor. The discharge causes frequent problems when the method is used with a conventional tank type crystallizer.

A need continues to exist for a means of overcoming the above-mentioned problems in the  $\alpha$ -APM crystallization step, i.e., preventing the crystals from forming on the heat transfer surface, decreasing investment in equipment by using an existing or widely-used crystallizer and improving the solid-liquid separability of the crystal slurry.

## SUMMARY OF THE INVENTION

Accordingly, one object of the present invention is to provide a process which overcomes the problem of crystal formation on the cooling surface of an  $\alpha$ -APM crystalliz system (crystallizer).

This and other objects which will become apparent from the following specification have been achieved by the present process. In the present process, when  $\alpha$ -APM is crystallized from its aqueous solution the pressure in the crystallizer is kept not higher than atmospheric pressure (760 Torr) so as to concentrate the solution by vaporizing the solvent, whereupon the solution is cooled by the latent heat of vaporization and is thereby crystallized.

## BRIEF DESCRIPTION OF THE DRAWING

Figure 1 shows a diagram of a crystallizer equipment, which can be used in the present invention and was used in Example 1.

## DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

A crystallization operation is generally carried out such that, per unit time, a vaporizing amount of the solvent (water) per vaporizing area of the concentrated solution (or slurry) is about 1,000 kg/

m<sup>2</sup>·h for the crystallization of ordinary substances other than α-APM. For crystallization of α-APM, however, it has been discovered that a substantial bubbling of the slurry with vaporization occurs under conventional vaporization conditions. This bubbling is especially pronounced when the starting solution is fed to the crystallizer so that the depth of the solution in the crystallizer is kept constant. It is difficult to continue the operation of the equipment under these conditions. It is particularly preferred to control the vaporizing rate to a surprisingly low rate of 40 kg/m<sup>2</sup>·h or less, more preferably 20 kg/m<sup>2</sup>·h or less, so that a long and stable operation is possible.

A higher upper limit for the vaporizing rate is possible when using a mixed solvent of water and a lower alcohol, such as methanol or ethanol, than when using water alone. Further, when using a mixed solvent, equipment productivity is improved as the solubility of α-APM in the mixed solvent over 40°C is higher than in water alone, and thus the crystals obtained have larger diameters and good solid-liquid separability. As the apparatus for the present invention, any industrially employable existing or widely-used crystallizer, such as a general stirring crystallizer, a DTB (Draft Tube Battled) crystallizer, a crystal-Oslo crystallizer or modifications thereof may be used, so long as they have an enclosed structure capable of withstanding the reduced pressure used in the present method. The pressure in the crystallizer is kept at 100 Torr or less, preferably, 50 Torr or less.

Crystallizers are available without heat transfer surfaces for cooling. It is preferable to equip such crystallizers with a heat transfer means such as coils, jackets and so on, or with an external heat exchanger whereby the solution can be heated by circulating a part of the α-APM solution through the heat transfer means. Heating the α-APM solution is preferable when the temperature of the solution becomes too low. When the temperature of the solution becomes too low, the vaporization rate is lowered, thereby decreasing the efficiency of the present process. Although the temperature of operation during the present process depends on the operation pressure, it is preferable to keep the temperature of the solution at 20°C or lower (the lower limit is the freezing point of the solvent) to obtain maximum stability of the process and high yield of α-APM.

The starting α-APM solution may be fed to the crystallizer continuously, batchwise or as a combination of batch and continuous operation. It is preferable in view of equipment productivity and yield to feed the α-APM solution continuously keeping the depth of the solution constant. In this case, the yield per equipment volume can be increased by simultaneously discharging the con-

centrated solution or slurry (continuous vaporization operation).

Since the bubbling is remarkable as mentioned above, especially when using water as a solvent, it is necessary to control the vaporizing rate to 40 kg/m<sup>2</sup>·h or less, preferably 20 kg/m<sup>2</sup>·h or less, or to use an aqueous mixed solvent containing a lower alcohol, preferably a C<sub>1-6</sub> alkyl alcohol. Methanol and ethanol are preferably used as the lower alcohol. Methanol is the most preferred lower alcohol since α-APM can undergo ester exchange reactions under some conditions reducing the overall yield of the process. The solid-liquid separability of the crystals deteriorates if the alcohol concentration is too high. Therefore, the alcohol concentration is preferably in the range of from 10 - 60% by volume of the solvent.

The concentration of α-APM in the starting solution is preferably a saturated solution in the solvent used at 30°C or higher, e.g. the solubility of α-APM at 30°C is 1-3 g/dl, since a dilute solution requires greater concentration to effect precipitation. The solubility of α-APM increases at higher temperatures, however, decomposition of α-APM simultaneously occurs, so, the maximum concentration of the starting solution should be the concentration of a saturated solution at 80°C, for example. A preferred range of the concentration of α-APM in the starting solution is 2-15 %, more preferably 3-10 %.

The present method of crystallizing α-APM overcomes deposition problems during crystallization. The use of water or an aqueous solvent containing a lower alcohol in the present process substantially improves the solid-liquid separability of α-APM crystals and also noticeably improves the yield of crystals. The present method has practical utility due to its simplicity and the use of conventional equipment.

Other features of the invention will become apparent in the course of the following description of exemplary embodiments which are given for illustration of the invention and are not intended to be limiting thereof.

## EXAMPLES

The test for evaluating the filterability of α-APM crystals obtained in the Examples is described below.

### Method of Measuring Filtration Specific Cake Resistance

One liter of a sample to be tested was sampled and filtered through a top-feed suction filter system (leaf tester). The pressure difference during filtration was 70 mmHg, which was kept constant

throughout the period of filtration. From the start of filtration, the amount of the filtrate V(ml) was measured at regular intervals and plotted on a graph having the amount of the filtrate as the horizontal axis and the value  $\theta/V$ , obtained by dividing the time of filtration  $\theta$  (s) by the amount of the filtrate, as the vertical axis. The slope of the line  $K(s/m^2)$  was obtained by the least square method. The value  $C'$ , obtained by dividing the total amount (g) of the crystals in the slurry by the total amount ( $cm^3$ ) of the liquid in the slurry, was used in the following equation, where filtration area A is 93 ( $cm^2$ ) and the viscosity  $\mu$  of the filtrate is 0.0135 (g/cm.s). The specific cake resistance  $\alpha$  (m/kg) thus calculated is a measure of the filterability of the sample. Samples having a lower value  $\alpha$  are more easily filtered.

#### Equation for Specific Cake Resistance

$$\alpha = 20.K.A^2.PT/\mu.C' \text{ (m/kg)}$$

where  $\alpha$  is the specific cake resistance (m/kg) of the filtered cake;

$\mu$  is the viscosity of the filtrate (g/cm.s) ;

PT is the pressure difference (dyne/cm<sup>2</sup>) of the filtered cake and the filtration device =  $\Delta P$  (mmHg)  $\times 1333.22$ ;

A is the filtration area ( $cm^2$ ); and

$C'$  is the weight of the crystals per unit volume of the liquid component in the slurry (g/ml) = dry cake weight (g)/(wet cake weight (g) - dry cake weight (g) + amount of final filtrate (ml)).

#### Example 1:

A pilot plant system having the configuration shown in Fig. 1 was used. An aqueous  $\alpha$ -APM solution having an  $\alpha$ -APM concentration of 4.5 wt% and a liquid temperature of 65°C was fed into the 200-liter jacketed crystallizer (1), the inner pressure in the crystallizer was kept at from 8 to 10 Torr by an external pressure-reducing device (2), and the liquid temperature in the crystallizer was kept at 10°C by the latent heat of vaporization without cooling or heating. The vaporizing rate of the water solvent was 40 kg/m<sup>2</sup>·h, and the slurry was discharged simultaneously so that the solution level in the tank was 50 %. The circulating speed of the solution was from 3 to 4 m<sup>3</sup>/h. The operation was continued for 24 hours, whereupon no rapid foaming occurred during the operation and the slurry had good fluidity. The specific resistivity value of the slurry obtained was  $7 \times 10^{10}$  (m/kg). After being filtrated with a small centrifuge followed by dewatering for 15 minutes, the crystals had a moisture content of 65 %.

#### Example 2:

The same experiment as that in Example 1 was repeated, except that the vaporizing rate of the water solvent was varied to 20 kg/m<sup>2</sup>·h. The operation was continued for 24 hours, whereupon no rapid bubbling or foaming occurred during the operation and the slurry had good fluidity. The specific cake resistance value of the slurry obtained was  $5.0 \times 10^{10}$  m/kg. After dewatering for 15 minutes, the crystals had a moisture content of 62.1%.

#### Comparative Example 1

The same operation as Example 1 was carried out except that a vaporizing rate of 100 kg/m<sup>2</sup>·h was used. Just after the start of the operation the surface of the solution rose about one meter and it became difficult to continue the operation. The operation was stopped after 5 hours.

#### Example 3:

The same apparatus as used in Example 1 was used. An aqueous 30% methanol solution of  $\alpha$ -APM having an  $\alpha$ -APM concentration of 4.3 wt% and a liquid temperature of 50°C was fed into the crystallizer (1) at a feed speed of 188 liter/h (average), the inner pressure in the crystallizer was kept at about 30 Torr using the external pressure-reducing device (2), and the liquid temperature in the crystallizer was kept at 20°C. The vaporizing rate of the solvent was 53 kg/m<sup>2</sup>·h, and the slurry was discharged at a rate of 176 liter/h (average) to keep the slurry level constant. The operation was continued for 24 hours, whereupon no rapid foaming occurred during the operation and the slurry had good fluidity. The specific cake resistance value of the slurry obtained was  $8.6 \times 10^9$  m/kg. After dewatering for 15 minutes with a centrifuge, the crystals had a moisture content (loss on dry) of 44 %.

#### Example 4:

The same apparatus as used in Example 1 was used. An aqueous 30% methanol solution of  $\alpha$ -APM having an  $\alpha$ -APM concentration of 3.7 wt% and a liquid temperature of 20°C was fed into the crystallizer (1) at a feed speed of 237 liter/h (average), and the inner pressure in the crystallizer was kept at about 30 Torr using the external pressure-reducing device (2). A part of the  $\alpha$ -APM solution was removed from the crystallizer and heated with an external heat exchanger (3), to keep the liquid temperature in the crystallizer at 20°C. The concentration ratio was controlled to 0.8. The vaporizing rate of the solvent was 160 kg/m<sup>2</sup>·h,

and the circulating speed of the solution was 0.4 m<sup>3</sup>/h. The operation was continued for 24 hours, whereupon no rapid foaming occurred during the operation and the slurry had good fluidity. The specific cake resistance value of the slurry obtained was  $2.8 \times 10^9$  m/kg. After dewatering for 15 minutes with a centrifuge, the crystals had a moisture content (loss on dry) of 37.5%.

Obviously, numerous modifications and variations of the present invention are possible in light of the above teachings. It is therefore to be understood that within the scope of the appended claims, the invention may be practiced otherwise than as specifically described herein.

#### Claims

1. A method of crystallizing  $\alpha$ -L-aspartyl-L-phenylalanine methyl ester from an aqueous solvent solution thereof, comprising:

crystallizing  $\alpha$ -L-aspartyl-L-phenylalanine in a crystallizer, wherein the pressure in the crystallizer is maintained at not higher than atmospheric pressure to vaporize said solvent and cooling said solution by the latent heat of vaporization.

2. The method of Claim 1, wherein said pressure in the crystallizer is 100 Torr or less, preferably 50 Torr or less.

3. The method of Claim 1 or 2, wherein the temperature of said solution is 20°C or less during said crystallizing step.

4. The method of any of the Claims 1 to 3, further comprising heating said solution indirectly with a heat exchange means during said crystallizing step.

5. The method of any of the Claims 1 to 4, wherein said aqueous solvent solution is continuously fed to the crystallizer, maintaining a substantially uniform depth of solution in the crystallizer to form a concentrated slurry.

6. The method of Claim 5, further comprising continuously discharging said concentrated slurry from said crystallizer.

7. The method of any of the Claims 1 to 6, wherein the amount of the solvent vaporized per vaporization area of the said solution per unit time is 40 kg/m<sup>2</sup> or less, preferably 20 kg/m<sup>2</sup> or less.

8. The method of any of the Claims 1 to 7, wherein said solvent is a mixed solvent com-

prising water and a lower alcohol.

9. The method of Claim 8, wherein said solution is concentrated by evaporating a part of said solvent.

10. The method of Claim 9, wherein said lower alcohol is methanol.

11. The method of Claim 9, wherein the methanol concentration in said solution is from 10 to 60 % by volume.

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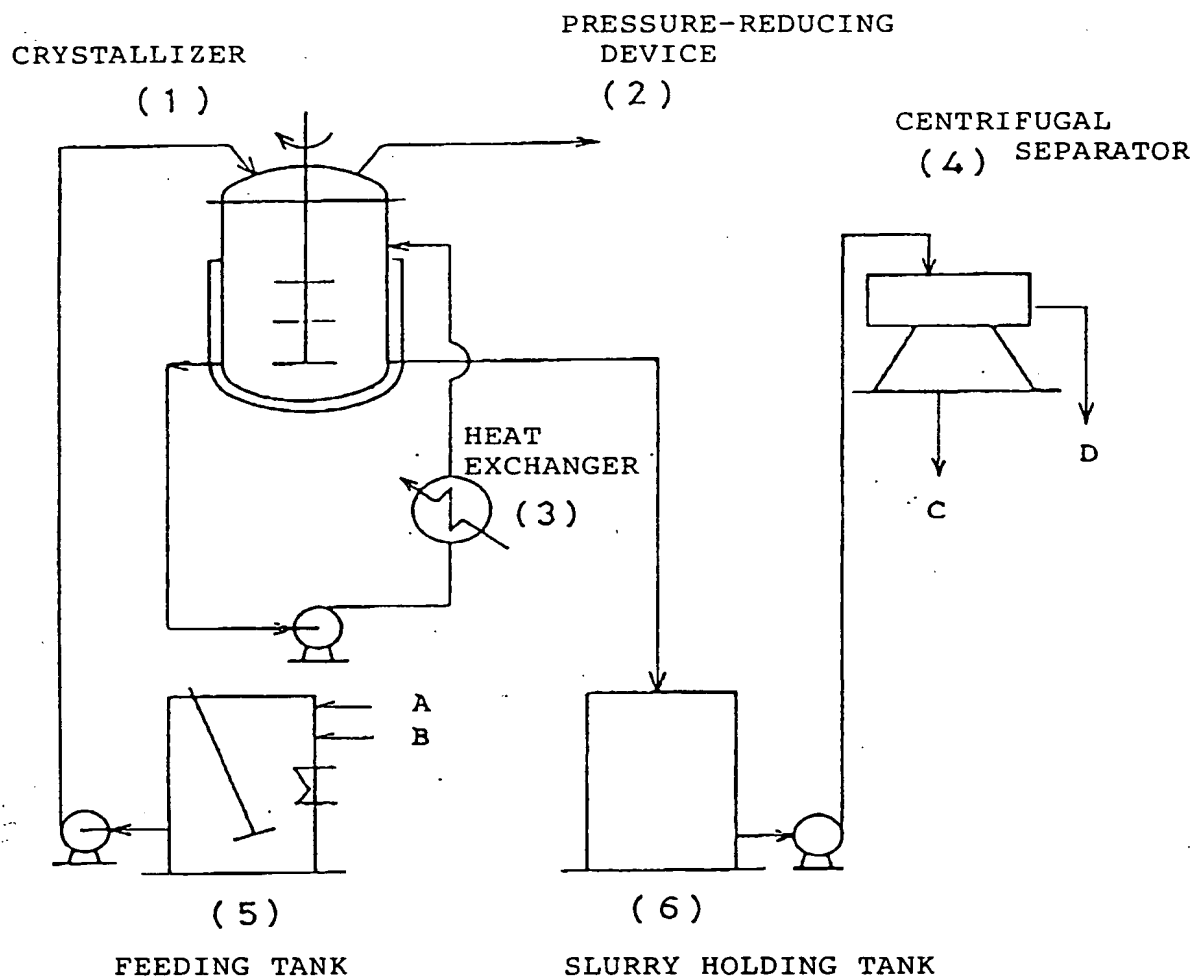
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FIG. 1



- A APM crystals
- B water, methanol
- C APM wet crystals
- D mother liquor





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## EUROPEAN SEARCH REPORT

Application Number

EP 92 10 8708

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
P, X	CHEMICAL ABSTRACTS, vol. 116, no. 1, 6 January 1992, Columbus, Ohio, US; abstract no. 5558M, A YAZAKI ET AL.: 'solubility-improved aspartame granules' page 556 ; column LEFT ; * abstract * & JP-A-03 204 895 (AJINOMOTO CO. INC.) 6 September 1991  -----	1-11	C07K5/06
			TECHNICAL FIELDS SEARCHED (Int. Cl.5)
			C07K
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 01 SEPTEMBER 1992	Examiner p. masturzo
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